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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/743,975	DAVYDOVA ET AL.	
	Examiner	Art Unit	
	Angela Bertagna	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *54-82* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *54-82* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/6/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

1. Applicant's submission of a substitute sequence listing on April 6, 2007 is acknowledged. The application is now in compliance with the Sequence Rules and will be examined on the merits. Also, it is noted that this application has been reassigned to Examiner Angela Bertagna in Art Unit 1637 whose correspondence information appears at the end of this office action.

Election/Restrictions

2. Applicant's election without traverse of Group I, claims 1-3, 7-47, and 49, in the reply filed on November 17, 2006 is acknowledged. In the response claims 1-53 were cancelled, and new claims 54-82 were presented. Claims 54-82 are within elected Group I, and therefore, they will be examined on the merits. Also, the previous requirement to elect a specific ligase, RNA polymerase, and promoter sequence is moot in view of the newly presented claims, and therefore, it has been withdrawn.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Priority

3. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 and 119(e) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed applications, Application No. 10/153,219 and Provisional Application 60/292,845, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. The prior-filed applications do not teach forming a transcription substrate by ligating linear single-stranded probe(s) hybridized to a target as required by independent claims 54, 78, and 81, and therefore, the prior-filed applications fail to adequately support the subject matter of the instant claims. Accordingly, the application has only been granted benefit of Provisional Application 60/436,062, filed December 23, 2002. This date has been used for prior art purposes.

Oath/Declaration

4. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:
Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c). The non-initialed and non-dated alterations appear on page 3 of the oath.

Information Disclosure Statement

5. Applicant's submission of an Information Disclosure Statement on November 6, 2006 is acknowledged. US 6,221,603 was listed twice on the IDS. The duplicate citation has been lined through.

Specification

6. The abstract of the disclosure is objected to because it is missing a period at the end of the last sentence. Correction is required. See MPEP § 608.01(b).

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. The hyperlinks appear in paragraphs 89, 163, and 223. Removal of the "http" would overcome this objection.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 54-80 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 54-80 are vague and indefinite, because independent claims 54 and 78 recite that target probes anneal adjacently to a target sequence. It is unclear from the claim language whether the target probes hybridize adjacently to one another on the target sequence or if the two probes and the target hybridize adjacently to one another on a fourth nucleic acid sequence. In other words, it is not clear from the claim language whether the probes hybridize to the target sequence or another sequence. If the claims are intended to describe hybridization of the probes adjacent to one another on the target sequence, insertion of "one another on" between "adjacently to" and "the target sequence" would overcome the rejection.

Claim 60 contains the trademark/trade names ICAN™, SPIA™, and Ribo-SPIA™. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the

trademark/trade name is used to identify/describe isothermal amplification methods and, accordingly, the identification/description is indefinite.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 54-58, 62, 73, 74, 81, and 82 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wenz et al. (US 2003/0119004 A1) as evidenced by Ullman et al. (US 5,815,243) in view of Falco et al. (Proceedings of the National Academy of Sciences, USA (1978) 75(7): 3220-3224; cited on IDS).

Wenz teaches methods for detecting a target nucleic acid comprising probe ligation and transcription.

Regarding claim 54, Wenz teaches a method for detecting a target nucleic acid comprising:

(a) providing one or more target probes comprising a linear single-stranded DNA molecule, the target probes comprising at least two target complementary sequences that are not joined to one another, wherein the 5'-end of a first target-complementary is complementary to the 5' end of the target nucleic acid sequence, and wherein the 3' end of a second target complementary sequence is complementary to the 3' end of the target nucleic acid sequence, and wherein the target probe that comprises the first target-complementary sequence also comprises a promoter that is joined to the 3' end of the first target-complementary sequence, wherein the promoter binds an RNA polymerase that can transcribe RNA using a single-stranded promoter (see Figure 4A and paragraphs 101 & 130-132)

(b) contacting the target probes with the target nucleic acid sequence and incubating under hybridization conditions, such that the target-complementary sequences anneal adjacently to one another on the target nucleic acid (see Figure 4 and paragraph 130)

(c) contacting the target probe-target complex with a ligase under ligation conditions to form a transcription substrate (see Figure 4 and paragraph 130; paragraph 82 teaches ligation using a ligase)

(d) contacting the transcription substrate with the RNA polymerase to form a transcription product (see Figure 4 and paragraph 130)

(e) detecting the transcription product (Figure 4 and paragraph 130).

Regarding claim 55, Wenz teaches repeating steps (a) – (e) (Figure 4 and paragraph 130; see also paragraphs 98-99).

Regarding claims 56 and 57, Wenz teaches that the target is a cDNA or DNA target in a sample (paragraphs 61-62 and 89).

Regarding claim 58, Wenz teaches that the target comprises a DNA sequence that is a product of an amplification reaction (see paragraph 89, where the cDNA resulting from reverse transcription is a product of an amplification reaction).

Regarding claim 62, Wenz teaches that the target probe comprising the second target-complementary sequence also comprises a signal sequence 5' of the target-complementary sequence (see Figure 4A and paragraph 130, where the signal probe contains a primer-specific portion and a sequence (ASSP) complementary to a probe on an addressable solid support).

Regarding claim 73, Wenz teaches providing two target probes (see Figure 4 and paragraph 130).

Regarding claim 74, Wenz teaches providing 3 target probes (paragraphs 75-78).

Regarding claim 81, Wenz teaches a method for detecting a target nucleic acid comprising:

(a) providing one or more target probes comprising a linear single-stranded DNA molecule, the target probes comprising at least two target complementary sequences that are not joined to one another, wherein the 5'-end of a first target-complementary is complementary to the 5' end of the target nucleic acid sequence, and wherein the 3' end of a second target complementary sequence is complementary to the 3' end of the target nucleic acid sequence, and wherein the target probe that comprises the first target-complementary sequence also comprises a

promoter that is joined to the 3' end of the first target-complementary sequence, wherein the promoter binds an RNA polymerase that can transcribe RNA using a single-stranded promoter (see Figure 4A and paragraphs 101 & 130-132)

(b) contacting the target probes with the target nucleic acid sequence and incubating under hybridization conditions, such that the target-complementary sequences anneal to the target nucleic acid to form a target-target probe complex (see Figure 4 and paragraph 130)

(c) contacting the target-target probe complex with a DNA polymerase under DNA polymerization conditions to form one or more DNA polymerase extension that are adjacent to the 5' end of a target probe, such that a complex is formed (see paragraph 94, where Wenz teaches gap-filling ligation). As evidenced by Ulmann et al., gap-filling ligation requires polymerase extension to fill gap between two adjacently hybridized probes such that the probes are adjacent to one another prior to ligation (see column 15, lines 10-58)

(d) contacting the target probe-target complex with a ligase under ligation conditions to form a transcription substrate (see Figure 4 and paragraph 130; paragraph 82 teaches ligation using a ligase)

(e) contacting the transcription substrate with the RNA polymerase to form a transcription product (see Figure 4 and paragraph 130)

(f) detecting the transcription product (Figure 4 and paragraph 130).

Regarding claim 82, Wenz teaches repeating steps (a) – (f) (Figure 4 and paragraph 130; see also paragraphs 98-99).

Wenz teaches that an RNA polymerase used to practice the invention is capable of using a single-stranded promoter for transcription (see Figure 4, paragraph 101, and paragraph 131),

but does not teach that the polymerase also lacks helicase-activity. It is noted that the polymerases taught by Wenz in paragraph 101 (T7 RNAP, SP6 RNAP, and T3 RNAP) possess helicase activity.

Falco describes the template requirements of the N4 virion RNA polymerase. Regarding claims 54 and 81, Falco teaches that the N4 virion RNA polymerase is capable of transcribing RNA using a single-stranded promoter (see abstract, pages 3221-3222, and Table 1). Falco further teaches that the N4 virion RNA polymerase lacks helicase activity (see page 3223, where the requirement of DNA gyrase for transcription indicates that the polymerase lacks helicase activity).

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to utilize the N4 virion RNA polymerase when practicing the method of Wenz. Since Wenz taught transcription using an RNA polymerase capable of transcribing RNA using a single-stranded promoter (Figure 4 and paragraphs 101 and 130-131), an ordinary practitioner would have been motivated to use any RNA polymerase known to possess such activity to practice the method recognizing its suitability for the intended purpose. As noted in MPEP 2144.07, selection of a known material based on its suitability for the intended purpose is prima facie obvious in the absence of secondary considerations. Also, as noted in MPEP 2144.06, it is prima facie obvious to substitute art-recognized equivalents useful for the same purpose. In this case, the N4 virion RNA polymerase was known to be capable of transcribing RNA using a single-stranded promoter, and therefore, the ordinary practitioner of the method taught by Wenz would have been motivated to utilize this polymerase to practice the method with a reasonable

expectation of success. Therefore, the methods of claims 54-58, 62, 73, 74, 81, and 82 are prima facie obvious in view of the combined teachings of Wenz as evidenced by Ullman and Falco.

10. Claims 59 and 78-80 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wenz et al. (US 2003/0119004 A1) as evidenced by Ullman et al. (US 5,185,243) in view of Falco et al. (Proceedings of the National Academy of Sciences, USA (1978) 75(7): 3220-3224; cited on IDS) and further in view of Lizardi et al. (US 6,316,229 B1; cited on IDS).

The combined teachings of Wenz, Ullman, and Falco result in the method of claim 54 as discussed above.

Regarding claim 78, Wenz teaches a method for detecting a target nucleic acid comprising:

(a) providing one or more target probes comprising a linear single-stranded DNA molecule, the target probes comprising at least two target complementary sequences that are not joined to one another, wherein the 5'-end of a first target-complementary is complementary to the 5' end of the target nucleic acid sequence, and wherein the 3' end of a second target complementary sequence is complementary to the 3' end of the target nucleic acid sequence, and wherein the target probe that comprises the first target-complementary sequence also comprises a promoter that is joined to the 3' end of the first target-complementary sequence, wherein the promoter binds an RNA polymerase that can transcribe RNA using a single-stranded promoter (see Figure 4A and paragraphs 101 & 130-132)

(b) contacting the target probes with the target nucleic acid sequence and incubating under hybridization conditions, such that the target-complementary sequences anneal adjacently to one another on the target nucleic acid (see Figure 4 and paragraph 130)

(c) contacting the target probe-target complex with a ligase under ligation conditions to form a transcription substrate (see Figure 4 and paragraph 130; paragraph 82 teaches ligation using a ligase)

(d) contacting the transcription substrate with the RNA polymerase to form a transcription product (see Figure 4 and paragraph 130)

(e) detecting the transcription product (Figure 4 and paragraph 130).

Regarding claim 79, Wenz teaches teaches releasing the catenated ligation product that is the transcription substrate from the target prior to transcription (see Figure 4 and paragraph 130).

Regarding claim 80, Wenz teaches repeating steps (a) – (e) (Figure 4 and paragraph 130; see also paragraphs 98-99).

Wenz does not teach that the target nucleic acid is a product of a rolling circle replication reaction as required by claims 59 and 78-80.

Lizardi teaches methods for rolling circle amplification. The methods of Lizardi comprise rolling circle replication followed by transcription (see Figure 8 and column 61, lines 22-67).

Regarding claim 78, Lizardi teaches a method comprising:

(a) providing a target sequence amplification (TSA) probe comprising a linear single-stranded DNA molecule having a 5' and 3' target-complementary portion, wherein the 5' and 3'

target-complementary regions are not joined to each other (see Figure 8, column 5, line 66 – column 6, line 4, and column 74, lines 30-49)

(b) providing a primer that is complementary to the TSA probe (see Figure 8, column 5, line 66 – column 6, line 4, and column 74, lines 61-62)

(c) contacting the TSA probe with the target under hybridization conditions such that the end portions anneal adjacently to the target sequence (see Figure 8, column 5, line 66 – column 6, line 4, and column 74, lines 37-49)

(d) ligating the hybridized TSA probe to form a closed circle (column 74, lines 50-56)

(e) forming a TSA circle-primer complex and conducting rolling circle replication under strand displacing conditions to generate multiple copies of the target (see Figure 8 and column 74, lines 57-65, where phi29 polymerase has strand displacement activity)

(f) hybridizing unligated target probes comprising two-target complementary portions at the 5' and 3' end to the resulting rolling circle replication products, conducting in vitro transcription using an RNA polymerase, and detecting the resulting product (see Figure 8 and column 74, line 65 – column 75, line 30; see also column 61, lines 22-67).

Lizardi teaches that rolling circle replication is a highly sensitive process capable of detecting single molecules (column 3, lines 58-63). Lizardi also teaches that the method generates a large amount of product orders of magnitude higher than PCR amplification methods (column 3, line 65 – column 4, line 3).

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to apply the teachings of Lizardi to the method resulting from the combined teachings of Wenz, Ullman, and Falco. An ordinary practitioner would have been motivated to conduct

rolling circle replication as taught by Lizardi prior to conducting the ligation-dependent transcription reaction in the method of Wenz, since Lizardi taught that rolling circle replication was a highly sensitive method for generating a large amount of template to be used in subsequent amplification reactions such as a transcription reaction (see column 3, line 58 – column 4,line 3). Therefore, an ordinary practitioner would have been motivated to amplify the target by rolling circle replication as taught by Lizardi in order to generate a larger amount of template for the ligation-dependent transcription step, ultimately improving the sensitivity of the assay. Therefore, the methods of claims 59 and 78-80 are prima facie obvious in view of the combined teachings of Wenz, Ullman, Falco, and Lizardi.

11. Claim 60 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wenz et al. (US 2003/0119004 A1) as evidenced by Ullman et al. (US 5,185,243) in view of Falco et al. (Proceedings of the National Academy of Sciences, USA (1978) 75(7): 3220-3224; cited on IDS) and further in view of Weier et al. (Biotechniques (1990) 8(3): 252-254, 256, 257).

The combined teachings of Wenz, Ullman, and Falco result in the method of claim 58, as discussed above.

Regarding claim 60, the above references do not teach that the is target the result of a PCR amplification step.

Weier teaches methods for generating DNA templates for transcription reactions. Regarding claim 60, Weier teaches using PCR to generate the DNA templates. Weier teaches that PCR generates large amounts of linear template DNA for transcription and eliminates the need for purification of plasmid DNA from cells (see abstract and page 252, columns 2-3).

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to prepare DNA templates for use in the ligation-dependent transcription reaction taught by Wenz using PCR. An ordinary practitioner would have been motivated to do so, since Weier taught that PCR generated a large amount of linear template DNA for transcription without the need for plasmid purification from cells. An ordinary practitioner would have recognized that this method of template preparation was faster and simpler than conventional purification methods, and therefore, would have been motivated to utilize it in the method of Wenz. Therefore, the method of claim 60 is prima facie obvious in view of the combined teachings of Wenz, Ullman, Falco, and Weier.

12. Claims 61, 66-68, 71, and 72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wenz et al. (US 2003/0119004 A1) as evidenced by Ullman et al. (US 5,185,243) in view of Falco et al. (Proceedings of the National Academy of Sciences, USA (1978) 75(7): 3220-3224; cited on IDS) and further in view of Zhang et al. (US 5,876,924).

The combined teachings of Wenz, Ullman, and Falco result in the method of claim 54, as discussed above.

None of the above references teach the use of bipartite probes as required by claims 61, 66-68, 71, and 72.

Zhang teaches a method for detecting target nucleic acids comprising hybridization of a bipartite probe comprising 5' and 3' terminal target-complementary portions and also an RNA polymerase promoter sequence to a target sequence, ligation of the bipartite probe to form a closed circular probe, and transcription of the closed circular probe using RNA polymerase (see

Figure 20 and column 24, line 59 – column 25, line 2). Zhang teaches that these bipartite probes having a target-complementary region at the 5' and 3' ends provide increased specificity and more efficient amplification and detection of target sequences (column 19, lines 7-19).

Regarding claims 61, 66 and 71, the probe taught by Zhang is a bipartite probe comprising two target-complementary sequences that anneal adjacently to one another on a target sequence (see Figure 20 and column 22, line 66 – column 23, line 22).

Regarding claims 67 and 68, the bipartite probe taught by Zhang comprises a promoter target probe and a signal target probe (see Figure 20 and column 24, lines 59-66). The probe of Zhang comprises a signal probe comprising a signal sequence located 5' of the second (3') target-complementary portion, because any of the sequences in the non-target-complementary portion of the probe are detectable (e.g. via hybridization with a complementary probe). The specification defines a "signal sequence" as a sequence capable of being detected (see paragraph 143 of the specification on page 60). Since any stretch of nucleic acid sequence contained in the circular probe is inherently detectable (e.g. by hybridization with a complementary probe), the circular probe of Zhang contains a signal sequence.

Regarding claim 72, Zhang teaches the use of a single bipartite probe (see Figure 20).

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to apply the teachings of Zhang to the method resulting from the combined teachings of Wenz, Ullman, and Falco. An ordinary practitioner would have been motivated to substitute the bipartite probe of Zhang for the monopartite probes taught by Wenz, since Zhang taught that bipartite probes improved the specificity of the assay and also the increased the efficiency of amplification and detection (column 19, lines 7-19). Therefore, the methods of claims 61, 66-68,

71, and 72 are prima facie obvious in view of the combined teachings of Wenz, Ullman, Falco, and Zhang.

13. Claim 63 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wenz et al. (US 2003/0119004 A1) as evidenced by Ullman et al. (US 5,185,243) in view of Falco et al. (Proceedings of the National Academy of Sciences, USA (1978) 75(7): 3220-3224; cited on IDS) and further in view of Tyagi et al. (Proceedings of the National Academy of Sciences, USA (1996) 93: 5395-5400).

The combined teachings of Wenz, Ullman, and Falco result in the method of claim 62, as discussed above.

Wenz, Ullman, and Falco do not teach that the signal sequence encodes a substrate for Qbeta replicase as required by claim 63.

Tyagi teaches methods for detection of nucleic acids comprising hybridization of a left and right target-complementary probe to a target nucleic acid followed by ligation and replication using Qbeta replicase (see Figures 1-2 and pages 5397-5398). Regarding claim 63, the probes of Tyagi comprise a substrate for Qbeta replicase. Tyagi teaches that Qbeta replicase-based detection is simple, does not require primers or separation of the hybridized ligated probe from the target sequence by thermal denaturation, and is extremely sensitive (page 5395, column 2).

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to utilize a Qbeta replicase substrate as the signal sequence in the probes taught by Wenz. An ordinary practitioner would have been motivated to do so since Tyagi taught that

Qbeta replicase-based detection of ligated probes hybridized to a target nucleic acid was simple, required neither exogenous primers nor thermal denaturation, and was extremely sensitive (page 5395). Therefore, the method of claim 63 is prima facie obvious in view of the combined teachings of Wenz, Ullman, Falco, and Tyagi.

14. Claim 64 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wenz et al. (US 2003/0119004 A1) as evidenced by Ullman et al. (US 5,185,243) in view of Falco et al. (Proceedings of the National Academy of Sciences, USA (1978) 75(7): 3220-3224; cited on IDS) and further in view of Campbell (US 5,683,888).

The combined teachings of Wenz, Ullman, and Falco result in the method of claim 62, as discussed above.

Wenz, Ullman, and Falco do not teach that the signal sequence encodes green fluorescent protein as required by claim 64.

Campbell teaches methods of detecting biological molecules of interest based on bioluminescence generated from a rainbow protein (see column 4, lines 37-46). Campbell also teaches in Example 8 a method for directly detecting a target nucleic acid comprising conducting an amplification reaction using a first primer comprising a target-specific portion and SP6 RNAP promoter and a second primer coupled to a GFP cDNA sequence, transcribing and translating the resulting products, and detecting GFP bioluminescence to directly detect the target (see column 7, line 50 – column 8, line 17).

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to incorporate a GFP-encoding sequence into the signal probe of Wenz. An ordinary

practitioner would have been motivated to do so since Campbell taught that such a primer permitted direct detection of transcribed (and translated products) based on sensitive luminescence measurements. Since the GFP cDNA sequence was known in the art and Campbell taught that the method was applicable to detection of diverse targets (column 4, lines 37-46), an ordinary practitioner would have had a reasonable expectation of success in applying the teachings of Campbell to the method of Wenz. Accordingly, the method of claim 64 is prima facie obvious in view of the combined teachings of Wenz, Ullman, Falco, and Campbell.

15. Claim 65 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wenz et al. (US 2003/0119004 A1) as evidenced by Ullman et al. (US 5,185,243) in view of Falco et al. (Proceedings of the National Academy of Sciences, USA (1978) 75(7): 3220-3224; cited on IDS) and further in view of Zhang et al. (US 5,876,924) and further in view of Moran et al. (Nucleic Acids Research (1996) 24(11): 2044-2052).

The combined teachings of Wenz, Ullman, Falco, and Zhang result in the method of claim 61, as discussed above.

None of the above references teaches that the bipartite target probe comprises a transcription termination sequence 5' of the second target complementary sequence as required by claim 65.

Moran teaches methods for conducting in vitro transcription reactions. Moran teaches that in conventional run-off transcription assays the 3' end of the transcription product is often poorly defined, because RNA polymerase often adds one or more additional nucleotides to the RNA chain (page 2044). Moran teaches that this complicates purification, may interfere with

subsequent reactions, such as ligation, and wastes nucleotide substrates (page 2044, column 2). Moran teaches that "addition of a single non-coding nucleotide analogue to the 5' terminus of the template DNA strand can result in much more efficient and specific termination at the desired site (3'-end of the product). The use of such 'terminator' nucleotides results in the production of cleaner RNA and DNA oligonucleotide products, often in greater yields, and with more efficient use of nucleotides (page 2044, column 2 – page 2045, column 3).

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to include a transcription termination sequence 5' of the second target-complementary sequence when practicing the method resulting from the combined teachings of Wenz, Ullman, Falco, and Zhang. An ordinary practitioner would have been motivated to do since Moran taught that addition of a terminator nucleotide at the 5' end of a DNA template improved subsequent transcription reactions by reducing template-independent addition of nucleotides by RNA polymerase after reaching the end of the template, thus resulting in a cleaner product, produced in greater yield and with less waste of nucleotide substrates (pages 2044-2045). Therefore, the method of claim 65 is prima facie obvious in view of the combined teachings of Wenz, Ullman, Falco, Zhang, and Moran.

16. Claim 69 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wenz et al. (US 2003/0119004 A1) as evidenced by Ullman et al. (US 5,185,243) in view of Falco et al. (Proceedings of the National Academy of Sciences, USA (1978) 75(7): 3220-3224; cited on IDS) and further in view of Zhang et al. (US 5,876,924) and further in view of Tyagi et al. (Proceedings of the National Academy of Sciences, USA (1996) 93: 5395-5400).

The combined teachings of Wenz, Ullman, Falco, and Zhang result in the method of claim 68, as discussed above.

Wenz, Ullman, Falco, and Zhang do not teach that the signal sequence encodes a substrate for Qbeta replicase as required by claim 69.

Tyagi teaches methods for detection of nucleic acids comprising hybridization of a left and right target-complementary probe to a target nucleic acid followed by ligation and replication using Qbeta replicase (see Figures 1-2 and pages 5397-5398). Regarding claim 69, the probes of Tyagi comprise a substrate for Qbeta replicase. Tyagi teaches that Qbeta replicase-based detection is simple, does not require primers or separation of the hybridized ligated probe from the target sequence by thermal denaturation, and is extremely sensitive (page 5395, column 2).

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to utilize a Qbeta replicase substrate as the signal sequence in the probes resulting from the combined teachings of Wenz, Ullman, Falco, and Zhang. An ordinary practitioner would have been motivated to do so since Tyagi taught that Qbeta replicase-based detection of ligated probes hybridized to a target nucleic acid was simple, required neither exogenous primers nor thermal denaturation, and was extremely sensitive (page 5395). Therefore, the method of claim 69 is prima facie obvious in view of the combined teachings of Wenz, Ullman, Falco, Zhang, and Tyagi.

17. Claim 70 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wenz et al. (US 2003/0119004 A1) as evidenced by Ullman et al. (US 5,185,243) in view of Falco et al.

(Proceedings of the National Academy of Sciences, USA (1978) 75(7): 3220-3224; cited on IDS) and further in view of Zhang et al. (US 5,876,924) and further in view of Campbell (US 5,683,888).

The combined teachings of Wenz, Ullman, Zhang, and Falco result in the method of claim 68, as discussed above.

Wenz, Ullman, Falco, and Zhang do not teach that the signal sequence encodes green fluorescent protein as required by claim 70.

Campbell teaches methods of detecting biological molecules of interest based on bioluminescence generated from a rainbow protein (see column 4, lines 37-46). Campbell also teaches in Example 8 a method for directly detecting a target nucleic acid comprising conducting an amplification reaction using a first primer comprising a target-specific portion and SP6 RNAP promoter and a second primer coupled to a GFP cDNA sequence, transcribing and translating the resulting products, and detecting GFP bioluminescence to directly detect the target (see column 7, line 50 – column 8, line 17).

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to incorporate a GFP-encoding sequence into the signal probe resulting from the combined teachings of Wenz, Ullman, Falco, and Zhang. An ordinary practitioner would have been motivated to do so since Campbell taught that such a primer permitted direct detection of transcribed (and translated products) based on sensitive luminescence measurements. Since the GFP cDNA sequence was known in the art and Campbell taught that the method was applicable to detection of diverse targets (column 4, lines 37-46), an ordinary practitioner would have had a reasonable expectation of success in applying the teachings of Campbell to the method resulting

from the combined teachings of Wenz, Ullman, Falco, and Zhang. Accordingly, the method of claim 70 is prima facie obvious in view of the combined teachings of Wenz, Ullman, Falco, Zhang, and Campbell.

18. Claims 75-77 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wenz et al. (US 2003/0119004 A1) as evidenced by Ullman et al. (US 5,185,243) in view of Falco et al. (Proceedings of the National Academy of Sciences, USA (1978) 75(7): 3220-3224; cited on IDS) and further in view of Sousa et al. (US 5,849,546) and further in view of Drolet et al. (US 6,280,943).

The combined teachings of Wenz, Ullman, and Falco result in the method of claim 54, as discussed above.

Wenz, Ullman, and Falco do not teach that the transcription product comprises AMP, GMP, 2'-fluoro-dUMP, and 2'-fluoro-dCMP.

Sousa teaches methods for generating transcription products using a mutant RNA polymerase and a mixture of canonical rNTP and non-canonical dNTP substrates (column 5, lines 26-56). Regarding claims 75-77, Sousa teaches that RNAse A only cleaves RNA after a C or a U, and therefore, replacement of these rNMPs with dNMPs or other nucleotides resistant to nuclease cleavage would prevent this cleavage by RNase A (column 8, lines 55-67). Sousa further teaches substitution of dNTPs with 2' fluoro or 2'amino groups (see column 7, lines 12-43, especially lines 38-43).

Drolet teaches methods for generating RNA ligands based on the SELEX method (see abstract and column 4, lines 29-40).

Regarding claims 75-77, Drolet teaches conducting in vitro transcription using dATP, dGTP, 2'-fluoro-UTP, and 2'-fluoro-CTP as substrates (column 10, line 61 – column 11, line 13). This results in a transcription product comprising AMP, GMP, 2'-fluoro-UMP, and 2'-fluoro-CMP. Drolet teaches that the 2'-fluoro substitution confers enhanced resistance to ribonucleases that utilize the 2'-hydroxyl moiety for cleavage of the phosphodiester bond (column 11, lines 8-11).

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to conduct the transcription reaction taught by Wenz using ATP, GTP, 2'-fluoro-dUTP, and 2'-fluoro-dCTP as nucleotide substrates. An ordinary practitioner would have been motivated to utilize these substrates in the transcription reaction since Sousa taught that dNMPs were resistant to RNase A digestion (column 8, lines 55-67), and Drolet taught that the 2'-fluoro substitution conferred enhanced resistance to ribonucleases that utilize the 2'-hydroxyl moiety for cleavage of the phosphodiester bond (column 11, lines 8-11). Although neither Sousa nor Drolet expressly teaches 2'-fluoro-dUTP and 2'-fluoro-dCTP, as noted in MPEP 2144.06, "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art. In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980)." In this case, Sousa and Drolet separately taught nucleotides resistant to ribonulcease digestion, dMNPs and 2'-fluoro-substituted nucleotides, respectively. Therefore, it would have been obvious for one of ordinary skill in the art to utilize a nucleotide substrate having both ribonuclease-resistant features (a deoxyribose sugar) and a 2'-fluoro substitution to reduce

undesirable ribonuclease degradation of RNA transcription products. Thus, the method of claims 75-77 is prima facie obvious in view of the combined teachings of Wenz, Ullman, Falco, Sousa, and Drolet.

Double Patenting

19. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

20. Claims 54-59, 61-64, 66-74, and 78-82 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 67-73, 75-77, 79-86, 88-92, 94-98, and 100-104 of copending Application No. 10/744,815 in view of Wenz et al. (US 2003/0119004 A1).

The instant claims are drawn to methods of target-dependent transcription comprising ligation of probe(s) comprising two target-complementary portions followed by transcription as

discussed in greater detail above. The claims of the '815 application recite a method of target-dependent transcription that overlaps in scope with the method of the instant claims. Regarding the instant claims 54, 61, 66, 67, 71, 72, 78, and 81, claims 67, 75, 79, 81, 84, 88-90, 92, 94, 95, 96, 98, 100, 102, and 104 of the '815 application recite the use of bipartite probes comprising a 5' and 3' target-complementary sequence and also a promoter sequence. These probes are hybridized to the target sequence and ligated to form a closed circle probe that is subsequently transcribed by an RNA polymerase. Claims 84, 88, 94, and 100 of the '815 application further recite that the transcription step is conducted using an RNA polymerase that can transcribe RNA using a single-stranded promoter. Further regarding the instant claim 78 and also claims 58 and 59, claim 81 of the '815 application recites that the target nucleic acid is prepared by rolling circle amplification. Further regarding the instant claim 81, claim 79 of the '815 application recites conducting polymerase extension of the hybridized probes prior to ligation and transcription. Regarding the instant claims 55, 80, and 82, claims 69, 76, 80, 83, and 86 of the '815 application recite conducting multiple cycles of the method. Regarding the instant claims 56 and 57, claims 70 and 71 of the '815 application conducting multiple cycles of the method. Regarding the instant claims 62-64 and 68-70, claims 72, 73, and 77 of the '815 application recite probes with a 5' signal sequence that encodes a detectable protein or a substrate for Qβ-replicase. Regarding the instant claims 73 and 74, claims 68 and 85 of the '815 application recite providing additional target-complementary probes. The limitations of the instant claim 79 are recited in claims 82, 91, 97, and 103 of the '815 application.

The primary difference between the instant claims and those of the '815 application is that the claims of the instant application recite the use of an RNA polymerase capable of

transcribing RNA using a single-stranded promoter, whereas the claims of the '815 application recite annealing of an antisense promoter oligonucleotide to a probe containing a sense promoter sequence to form a double-stranded promoter substrate for transcription by RNA polymerase. However, it would have been prima facie obvious for one of ordinary skill in the art to utilize either method of generating a transcription substrate, since Wenz taught the use of RNA polymerases capable of transcribing RNA using a single-stranded promoter or a double-stranded promoter (see paragraphs 101 and 131). An ordinary practitioner would have been motivated to substitute one method of generating a transcription substrate for another recognizing that each method was suitable for the intended purpose - generation of a ligation-dependent transcription product. As noted in MPEP 2144.07, selection of a known product or process based on its suitability for the intended purpose is prima facie obvious. Therefore, the method of claims 54-59, 61-64, 66-74, and 78-82 is prima facie obvious over claims 67-73, 75-77, 79-86, 88-92, 94-98, and 100-104 of the '815 application in view of Wenz.

This is a provisional obviousness-type double patenting rejection.

Conclusion

No claims are currently allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Angela Bertagna whose telephone number is 571-272-8291. The examiner can normally be reached on M-F, 7:30 - 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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